ann. behav. med. (2016) 50:370–384
DOI 10.1007/s12160-015-9763-7

ORIGINAL ARTICLE

Dispositional and Situational Avoidance and Approach as Predictors of Physical Symptom Bother Following Breast Cancer Diagnosis

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Published online: 14 January 2016

Abstract
Background Few studies examine whether dispositional approach and avoidance coping and stressor-specific coping strategies differentially predict physical adjustment to cancer-related stress.
Purpose This study examines dispositional and situational avoidance and approach coping as unique predictors of the bother women experience from physical symptoms after breast cancer treatment, as well as whether situational coping mediates the prediction of bother from physical symptoms by dispositional coping.
Method Breast cancer patients (N=460) diagnosed within the past 3 months completed self-report measures of dispositional coping at study entry and of situational coping and bother from physical symptoms every 6 weeks through 6 months.
Results In multilevel structural equation modeling analyses, both dispositional and situational avoidance predict greater symptom bother. Dispositional, but not situational, approach predicts less symptom bother. Supporting mediation models, dispositional avoidance predicts more symptom bother indirectly through greater situational avoidance. Dispositional approach predicts less symptom bother through less situational avoidance.
Conclusion Psychosocial interventions to reduce cancer-related avoidance coping are warranted for cancer survivors who are high in dispositional avoidance and/or low in dispositional approach.

Keywords Avoidance · Approach · Coping · Breast cancer · Physical symptoms

Electronic supplementary material The online version of this article (doi:10.1007/s12160-015-9763-7) contains supplementary material, which is available to authorized users.

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Extensive research exploring the means through which individuals maintain well-being in the face of stress suggests that the way individuals cope, or try to modify the stressful situation or their associated emotional reactions [1], is associated with subsequent physical health [2]. Coping responses are conceptualized as both dispositional reactions to various stressors and as situational responses to specific stressors. Understanding how the consequences of different coping strategies vary when they are employed routinely versus only in particular contexts has theoretical and clinical implications. However, dispositional and situational coping strategies most frequently are investigated independently, and empirical evidence regarding their relationship is limited. The current study investigates the relationship of dispositional approach and avoidance coping with emotional experiences, as well as situational approach and avoidance coping with cancer, with

bother from physical symptoms in the months following breast cancer diagnosis. Specifically, we examine the independent utility of dispositional and situational coping to predict bother from physical symptoms as well as the potential mediating role of situational coping in the relationship between dispositional coping and symptom bother.

Dispositional and Situational Coping

Whereas situational coping is a transactional process in which individuals change their coping response to meet the demands of specific life stressors [1], dispositional coping is conceptualized as habitual tendencies that shape the way individuals handle stress [3]. Intuitively, one might think that situational coping responses directly reflect dispositional coping styles. However, the small body of existing research suggests that the two constructs are related but not redundant [4]. Dispositional coping measures demonstrate greater stability over time than situational assessments [5]. Furthermore, dispositional coping predicts similar situational coping reliably, but the magnitude of the relations is often low [6]. In a study of undergraduates [6], dispositional coping styles were related to situational coping at approximately r=0.30. In its association with concurrent psychological distress, dispositional distancing-avoidance explained 25 % of the variance and situational distancing-avoidance explained an additional 6 % [4].

Moos and Holahan [7] developed a model that illustrates how dispositional and situational coping might work together to influence well-being. In this model, stable personal attributes (e.g., problem-solving styles) and stable environmental factors (e.g., chronic life stressors) impact physical and mental health directly and indirectly through situational coping. Thus, situational coping is theorized to mediate the relationship between dispositional coping and adjustment. Past research indicates that several dispositional variables, including self-esteem, mastery, and optimism, serve as antecedents to situational coping for a variety of stressors [8]. Regarding women with breast cancer, Carver et al. [9] found that the relationship between high dispositional optimism and low later distress was mediated by greater use of coping through acceptance and less use of coping through denial and behavioral disengagement. However, few studies to our knowledge have examined whether other dispositional variables predict situational coping, which could in turn mediate the relationship between dispositional coping tendencies and adjustment.

Avoidance and Approach Coping

Researchers often organize specific coping strategies into higher-order classifications [10]. An approach/avoidance classification is supported by factor analysis of published instruments to assess coping [11] and corresponds to more general approach and avoidance motivational systems that underlie behavior [12]. Avoidant coping involves cognitive or behavioral efforts to avoid stressor-related thoughts or feelings (e.g., withdrawal and denial). Approach-oriented coping involves efforts to accept, manage, and/or confront the stressor or associated emotional responses (e.g., seeking social support, problem solving, and positive reappraisal).

Avoidance typically predicts maladjustment under chronically stressful conditions [10, 13, 14] and, more specifically, in breast cancer patients [15, 16]. Research suggests that avoidance of thoughts and emotions paradoxically increases negative thoughts and results in psychological distress [17]. In the context of breast cancer, coping through avoidance prior to biopsy is associated with negative mood after cancer diagnosis and surgery [18]. Similarly, coping with breast cancer through avoidance is associated with increased psychological distress throughout the 12 months following surgery [9]. Additionally, individuals who report engaging in avoidance-oriented coping also are more likely to avoid talking to others about their cancer [19], avoid seeking information about their cancer, delay seeking medical consultation for cancer symptoms [20], and be more passive in medical decision-making [21], all of which could impact physical health-related adjustment negatively. In other diseases, avoidance of disease-related thoughts and feelings also is associated with poor medication adherence [22, 23].

Conversely, approach-oriented coping often predicts positive psychological and physical adjustment to stressors [24–26]. In breast cancer survivors, coping through emotional approach (i.e., expressing and processing cancer-related emotions) predicted increased vigor, fewer medical visits, and improved perceived health status and distress 3 months later [27]. In another study, women with breast cancer who reported an approach-oriented coping style reported fewer psychological and physical side effects than women who coped through avoidance [28]. Additionally, individuals who endorse high levels of approach-oriented coping strategies take a more active role in medical decision-making [21], seek more information about their cancer [29], and have shorter time intervals between symptom recognition and help-seeking [30], which could predict better physical health-related adjustment to breast cancer.

Breast Cancer and Physical Symptom Bother

The period following cancer diagnosis typically involves onerous medical treatment, disruptions to daily life, and negative emotional and physical sequelae [31]. Estimates suggest that over 40 % of cancer patients report experiencing multiple symptoms when undergoing active treatment [32]. Breast cancer treatments are associated with decreases in physical functioning and increases in several physical symptoms, including musculoskeletal pain, fatigue, and weight problems [33–35].

Such physical symptoms can persist for years after diagnosis (see [36] for a review). In women with breast cancer, 35 % report greater than average fatigue 1–5 years after diagnosis [37], 63 % of women experience persistent pain after surgical treatment [38], and 30–100 % of breast cancer survivors experience sexual complaints [39]. Distressing physical symptoms are associated with patients' quality of life, adherence to medical treatments, functional abilities, and mood [32].

Understanding how dispositional and situational coping relate to bother from physical symptoms in the early months following breast cancer diagnosis is required to develop better-targeted interventions that will improve patients' health and well-being. Beyond understanding how both dispositional and situational coping relate to bother from physical symptoms directly, it is important to determine whether situational coping is a mechanism through which dispositional coping influences symptom bother. Situational coping strategies may be more amenable to change through intervention, and by specifying who is most likely to employ maladaptive versus adaptive coping strategies, we can target interventions to at-risk individuals.

The current study examines two different models of the relationship between situational and dispositional coping in predicting breast cancer treatment-related bother from physical symptoms. First, a main effect model will be examined. It is hypothesized that both situational and dispositional avoidance coping will be associated independently with greater physical symptom bother. Additionally, it is hypothesized that both dispositional and situational approach coping will be associated with less physical symptom bother independently. Second, a mediation model will be tested. It is hypothesized that dispositional avoidance will be indirectly related to physical symptom bother through increased situational avoidance coping and decreased situational approach coping. Similarly, it is hypothesized that dispositional approach will be indirectly related to physical symptom bother through increased situational approach coping and decreased situational avoidance coping.

Method

Participants

Women (N=460) recently diagnosed with stages I–IV breast cancer were recruited within 3 months of diagnosis to participate in a larger study examining predictors of depression and other outcomes during the year following breast cancer diagnosis. The present study reports on the first five assessments (study entry through 6 months) from that ongoing observational longitudinal study [36]. As displayed in Table 1, on average, participants were 56 years old and 68 % were non-Latina white, whereas 19 % were Latina. Half were employed.

Procedures

Women were recruited from three oncology clinics in the greater Los Angeles area and one clinic at the University of Arizona Cancer Center. Interested women were identified through presentation of the study (within scheduling constraints) to consecutive newly diagnosed or newly recurrent breast cancer patients by clinic or research staff and, with verbal consent, contacted by study personnel to learn more about the study. Participants must have had a new or recurrent diagnosis of invasive breast cancer, enrolled in the study within the 3 months after their cancer diagnosis, and completed assessments in English. Any standard medical treatment for cancer was allowed (i.e., surgery, chemotherapy, radiotherapy, neoadjuvant chemotherapy, and endocrine therapy), and any additional medication was permitted. Exclusion criteria included current or past bipolar disorder, schizophrenia, schizoaffective disorder, current suicidality, younger than 21 years of age, no English literacy, or a cognitive disorder (e.g., dementia). Eligible participants were scheduled for an in-person study entry assessment within 3 months of their diagnosis and a follow-up telephone assessment every 6 weeks for 6 months (i.e., four 6-week follow-up assessments; two later follow-up assessments are not examined here).

Study Entry Assessment

Study procedures were approved by the University of California, Los Angeles, and University of Arizona institutional review boards. The study entry session, lasting approximately 3 h, was completed in a private room at the treating oncology center or at women's homes. Trained post-baccalaureate-level members of the research team conducted the session. After giving informed consent, participants completed the measures described below and other measures not included in the current report. Women began by completing self-report measures in interview format but were given the option of completing the rest of the questionnaires independently on the computer with the interviewer present.

Six-Week Assessments

Every 6 weeks for 6 months after the study entry assessment, participants completed a follow-up phone assessment of physical and psychological health. Phone calls lasted approximately 30 min. Of the women who completed the study entry assessment (N=460), 428 (93 %) completed the week 6 assessment, 420 (91 %) completed the week 12 assessment, 411 (89 %) completed the week 18 assessment, and 411 (89 %) completed the week 24 assessment. Participants were able to rejoin the study at later time points if they missed a previous assessment. Overall attrition was low for a longitudinal study. Twelve women (3 %) dropped out or were lost to follow-up

Table 1 Sample characteristics and demographics (N=460)

Sample characteristics	Study entry M (SD)/N (%)	6-Week N (%)	12-Week N (%)	18-Week N (%)	24-Week N (%)
Age	56.35 (12.61)				
Ethnicity					
Asian	24 (5.20)				
White/European American	311 (67.60)				
Latina	89 (19.30)				
Black/African American	10 (2.20)				
Multiracial	8 (1.7)				
Other	18 (4.0)				
Income					
Less than $50,000	124 (28.50)				
$50,000–$74,999	97 (22.30)				
$75,000–$100,000	57 (13.10)				
More than $100,000	157 (36.10)				
Employment					
Employed	236 (52.10)				
Not employed	83 (18.30)				
Retired	134 (29.60)				
Education					
High school or less	114 (23.10)				
2-year college	91 (20.00)				
4-year college	164 (36.10)				
Advanced Degree	85 (18.80)				
Relationship status					
Significant other	317 (69.70)				
No significant other	138 (30.30)				
Study site					
Arizona	163 (35.4)				
Los Angeles	297 (64.6)				
Physical comorbidities	1.85 (1.88)				
Months since diagnosis	2.13 (0.81)	3.79 (1.01)	5.21 (1.14)	6.54 (1.03)	7.99 (1.01)
Stage					
1	197 (43.80)				
2	176 (39.10)				
3	52 (11.60)				
4	25 (5.60)				
Chemotherapy in the past 6 weeks	183 (41.7)	167 (42.3)	110 (28.4)	53 (13.8)	27 (7.0)
Surgery in the past 6 weeks	270 (59.6)	57 (14.4)	43 (11.1)	59 (15.4)	48 (12.5)
Taking estrogen antagonist	30 (6.6)	45 (11.5)	53 (13.8)	67 (17.5)	85 (22.1)
Taking aromatase inhibitor	37 (8.0)	64 (16.3)	71 (18.4)	75 (19.6)	79 (20.6)
Radiation therapy in the past 6 weeks	31 (7.0)	35 (8.9)	19 (4.5)	44 (11.5)	39 (10.1)
Herceptin use in the past 6 weeks	72 (15.9)	75 (19.1)	80 (20.7)	82 (21.4)	79 (20.5)
Completed last treatment in the last 6 weeks	112 (24.5)	54 (11.8)	48 (10.5)	75 (16.4)	168 (36.8)

between study entry and the 6-week assessment, 4 (1 %) between 6 and 12 weeks, 8 (2 %) between 12 and 18 weeks, and 5 (1 %) between 18 and 24 weeks. Binary logistic regression analyses revealed that study entry values of the dependent and predictor variables investigated in the present study did not predict later dropout (p>0.05). Complete information on

enrollment and attrition can be found in the parent study publication [40]. Women received $60 compensation for in-person assessments and $30 for phone assessments.

Measures

Dispositional Avoidance and Approach of Emotions

Avoidance

Dispositional avoidance (DispAVOID) was assessed using the six-item non-acceptance of emotion subscale of the Difficulties in Emotion Regulation Scale [41] completed at study entry. Scores range from 6 to 30 with higher total scores indicating greater tendency to reject negative emotions (e.g., "*When I am upset, I feel guilty for feeling that way*"). Participants rated how much they experience each item on a five-point Likert scale (1=*almost never* [0–10 %] and 5=*almost always* [91–100 %]). The non-acceptance of emotion subscale has high internal consistency (α=0.85) as well as adequate construct validity as demonstrated by positive correlations with experiential avoidance (r=0.39) and negative correlations with emotional expressivity (r=−0.14) and expectancy for negative mood (r=−0.42) [41]. The non-acceptance of emotion scale evidences adequate 4–8-week test-retest reli- ability (ρ_I=0.69; [41]). Internal consistency in this sample was α=0.91.

Approach

Dispositional approach (DispAPPROACH) was assessed using five items from the emotional acceptance subscale of the Control of Feelings Scale [42, 43] completed at study entry. Items were averaged. Scores range from 0 to 100, with higher scores indicating greater acceptance of emotion (e.g., "*I naturally and easily attend to my feelings*"). Participants responded in increments of 10 from 0=*not at all like me* to 100=*exactly like me*. The scale has strong test-retest reliability with average product-moment correlations of 0.87 [43]. Internal consistency in this sample was α=0.91.

Situational Avoidance and Approach Coping

Avoidance

Situational avoidance coping (SitAVOID) was assessed using 12 items from three COPE Inventory (COPE) [5] subscales (mental disengagement, behavioral disengagement, and denial) completed at each assessment, which have been used in previous studies (e.g., [27, 44]) to create a psychometrically sound measure of avoidance coping. Items were anchored to the experience of breast cancer. Participants rated how often they engaged in each item in the past 4 weeks on a four-point Likert scale from 1=*I do not do this at all* to 4=*I do this a lot*. Sample items include "*I turn to work or other substitute activities to take my mind off things*" (mental disengagement), "*I admit to myself that I cannot deal with it, and quit trying*" (behavioral disengagement), and "*I pretend that it has not really happened*" (denial). Items were averaged across the three subscales. Scores range from 1 to 4, with higher scores indicating greater avoidance of cancer-related thoughts and feelings. Past research indicates that the correlations between situational coping strategies are low to moderate over 1 week (r_{tt}=0.27–0.70), with an average correlation across subscales of r_{tt}=0.47 for both avoidance and approach strategies [6]. Additionally, avoidance subscales of the COPE have evidenced construct validity, as demonstrated by positive correlations with anxiety (r≥0.21) [5], for example. Across the five assessments in this study, internal consistency reliability was acceptable, with αs ranging from 0.73 to 0.78.

Approach

Situational approach coping (SitAPPROACH) was assessed using 24 items from six COPE [5] and Emotional Approach Coping (EAC) subscales [45] (COPE=problem-focused coping, acceptance, social support, and positive reinterpretation and EAC=emotional expression and emotional processing) completed at each assessment. Items were anchored to participants' experience of breast cancer. Participants rated how often they engaged in each item in the past 4 weeks on a four-point Likert scale from 1=*I do not do this at all* to 4=*I do this a lot*. Sample items include "*I think hard about what steps to take*" (problem-focused), "*I accept the reality of the fact that it happened*" (acceptance), "*I try to get advice from someone about what to do*" (social support), "*I take time to express my emotions*" (emotional expression), "*I delve into my feelings to get a thorough understanding of them*" (emotional processing), and "*I look for something good in what is happening*" (positive reinterpretation). Items were averaged across the six subscales. Scores range from 1 to 4, with higher scores indicating greater approach of the cancer experience. Approach subscales of the COPE and EAC have evidenced construct validity, as demonstrated by modest positive correlations with optimism (r=0.10–0.41) [5], for example. Across the five assessments, internal consistency reliability ranged from α=0.91 to 0.94.

Physical Symptom Bother

Breast Cancer Prevention Trial Symptom Scales

This 25-item self-report questionnaire evaluates physical symptom bother from common side effects of breast cancer treatment (e.g., surgery, chemotherapy, endocrine therapy, and

radiotherapy). Because the prevalence and impact of fatigue and problems with sexual functioning are notable [31, 37], the scale was expanded to include four items that assess bother from fatigue and sexual functioning. The Breast Cancer Prevention Trial (BCPT) Symptom Scales [46, 47] was completed at each assessment point. Each item is a different physical symptom (e.g., *hot flashes*, *nausea*, *bladder control*, *vaginal dryness*, *general aches and pains*, *forgetfulness*, *weight gain*, *lymphedema*, and *tiredness*), and participants are asked to rate how much they were bothered by each symptom over the past 4 weeks on a five-point Likert scale ranging from 0=*not at all* to 4=*extremely*. Items were averaged. Scores range from 0 to 4, with higher scores indicating greater symptom bother. The BCPT has evidence of discriminant validity, as demonstrated by modest negative correlations with health-related quality of life [47, 48]. Although the total BCPT score was correlated with depressive symptoms (r=0.43), when dismantling the overall scale, only one of eight subscales (i.e., cognitive symptoms) was significantly correlated with depression (r=0.46). This suggests the BCPT captures unique information about symptom bother related to breast cancer treatment [48]. Internal consistency for the total scale in this sample ranged from α=0.82 to 0.85 across study assessments.

Demographic Information

Demographic and cancer-related variables

Demographic information (i.e., age, marital status, education, employment, ethnicity, income, subjective social status (obtained via SES ladder; [49]), recruitment site, menopausal status, body mass index, and number of physical comorbidities) was self-reported at study entry. Cancer-related variables (i.e., number of weeks since diagnosis, chemotherapy, endocrine therapy, surgery, radiation therapy, herceptin use, and study assessment at which last medical treatment occurred [coded 1–5 for at which of the five assessments their last treatment occurred]) were obtained through self-report at study entry and each follow-up assessment. Cancer stage was obtained via medical chart review at study entry and was filled in by self-report when the chart was unavailable.

Data Analysis

First, to characterize the sample, means and standard deviations were calculated for all study variables. Next, to assess the relationships between predictors (i.e., DispAVOID, DispAPPROACH, SitAVOID, and SitAPPROACH) and the dependent variable (i.e., BCPT) over each study assessment, Pearson's correlation coefficients between predictors and the outcome were calculated.

Because the data were hierarchical with five repeated study assessments nested within participants, multilevel structural equation modeling (MSEM; [50, 51]) was conducted using Mplus version 7.3. Two-tailed significance tests were used throughout, and a $p<0.05$ was considered statistically significant. MSEM allows the testing of the effects of time-varying and time-invariant (i.e., measured at one time point) predictors on a time-varying outcome. A two-level model with repeated measures (level 1) nested within individuals (level 2) was used. The dependent variable (i.e., BCPT) and situational coping measures (i.e., SitAVOID and SitAPPROACH) were assessed every 6 weeks and analyzed as level 1 variables. Given their assumed stable nature, dispositional measures (i.e., DispAVOID and DispAPPROACH) were assessed at study entry and analyzed as level 2 predictors. In addition to the usual linear regression parameters, MSEM can have a random intercept, capturing the variability between participants in starting points (in the present study, individual differences in study entry physical symptom bother) and random linear and quadratic terms (e.g., variability between participants in the linear and quadratic trajectory of physical symptom bother). Time was centered around the average number of months since diagnosis at study entry (M=2.13; SD=0.81), situational coping scales were centered around their respective overall grand mean, and the dispositional coping scales were standardized to produce more interpretable betas. Models were estimated with full information maximum likelihood [52], which incorporates cases with missing data on predictors. There was fairly minimal missingness on major study predictors, ranging from 2 to 17 % across study time points. Power analyses using an $n_{effective}$ technique [53] indicate that our sample of 460 women provides a high level of power (power≥0.90) to detect a small effect (R^2=0.02) of a level 2 predictor. Because level 1 predictors are repeatedly measured, power for models containing level 1 predictors will be even higher to detect similarly sized effects.

Models without predictors or covariates were fitted to determine the overall symptom trajectories of the BCPT Symptom Scales. Additionally, likelihood ratio tests [54] were conducted to test random intercept, linear, and quadratic terms; all significant variance components, as well as covariances between them, were retained in all models.

A combined theoretical and empirical approach was used to determine covariates for inclusion in the final model. First, a set of covariates was selected for their theoretical relationship with the dependent variable, physical symptom bother. Then, multilevel structural equation modeling was used to examine the relations of demographic and cancer-related variables on the trajectory of physical symptom bother over time. Only variables that evidenced a statistically significant relationship with physical symptom bother were retained as covariates in the final model. The following variables were analyzed as potential covariates: chemotherapy, endocrine therapy, surgery, radiation therapy, herceptin use, cancer stage, perceived social status, income, education, employment, age, body mass

index, race, marital status, recruitment site, physical comorbidities, and at which study assessment women underwent their last medical treatment. Time-varying covariates that were measured repeatedly (e.g., chemotherapy status) were analyzed as level 1 variables, and covariates that were measured once (e.g., income) were analyzed as level 2 variables. The covariate, its interaction with linear time, and its interaction with quadratic time were included. If higher-order terms were significant, they and all lower-order terms were included as covariates in the final model. If the higher-order terms were not significant, they were dropped one by one from the model. Variables were retained as covariates if they related significantly to physical symptom bother ($p<0.05$). See Table 1 for the coding scheme used for covariates. Reference groups for categorical variables can be seen in Table 3.

To test the main effect models, situational and dispositional variables (i.e., SitAVOID, DispAVOID, SitAPPROACH, and DispAPPROACH) and their interactions with linear and quadratic time were each separately added to the multilevel models containing covariates. Again, if higher-order terms were not significant, they were dropped. To examine the unique predictive utility of each predictor, the four coping predictors and their interactions with linear and quadratic time were then entered into a model simultaneously. Computation of change in modeled variance, an analog to R^2 change values in multiple regression, followed the approach outlined by Snijders and Bosker [55]. Modeled variance is the proportional reduction in the residual between-person or residual within-person variance component with the addition of a predictor of interest. As advised by Snijders and Boskers ([55], p. 358), for the purpose of "practical data analysis", R^2 values were calculated for models with random intercepts only.

Mediation analyses were conducted to examine situational coping variables (SitAVOID and SitAPPROACH) as mediators of the relationship between dispositional coping variables (DispAVOID and DispAPPROACH) and physical symptoms. Multilevel mediation analyses were conducted using MSEM, with the predictor variable (i.e., dispositional coping) at level 2 and the mediating variable (i.e., situational coping) and outcome (i.e., symptom bother) variable at level 1 (i.e., 2-1-1 mediation; [56, 57]). The indirect effect is defined as the product of the *a* and *b* paths at level 2 and is referred to in the results as *ab* (see Fig. 1 for a diagram of the model). The indirect path represents the relationship between dispositional coping and physical symptoms through situational coping at the between-person level. Analyses were conducted using R 3.1 [58] and Mplus 7.3 [50] via Mplus Automation 0.6–3 [59]. Models were conducted separately for each situational mediator of each dispositional effect. Minimally informative priors were used for all parameters, and convergence was determined using Gelman's scale reduction factor<1.02 from four independent chains [60] with at least 10,000 iterations. Parameter estimates are reported as posterior medians and 95 % credible intervals. Credible intervals that do not include zero indicate statistically significant mediation.

Results

Please see Table 2 for descriptive statistics for predictor and outcome variables. DispAVOID and SitAVOID were positively correlated at all time points ($r=0.22–0.31$, $p<0.001$), as were DispAPPROACH and SitAPPROACH ($r=0.23–0.34$, $p<0.001$). DispAVOID and SitAPPROACH were not significantly correlated at any time point ($p>0.05$), and DispAPPROACH and SitAVOID were only significantly related at study entry ($r=-0.11$, $p=0.01$). DispAVOID and DispAPPROACH were negatively correlated ($r=-0.26$, $p<0.001$). SitAVOID and SitAPPROACH were not significantly related at any time point ($p>0.05$). SitAVOID was significantly correlated across time points ($r=0.47–0.68$, $p<0.001$), with measurements farther apart in time sharing lower-magnitude correlations (e.g., SitAVOID at study entry and 24 weeks ($r=0.47$, $p<0.001$) than those close in time (18 and 24 weeks ($r=0.68$, $p<0.001$)). SitAPPROACH was significantly correlated across time points ($r=0.53–0.83$, $p<0.001$), with measurements farther apart in time sharing lower-magnitude correlations (e.g., SitAPPROACH at study entry and 24 weeks ($r=0.53$, $p<0.001$)) than those close in time (18 and 24 weeks ($r=0.83$, $p<0.001$)). DispAVOID was significantly correlated with BCPT at all study time points ($r=0.17–0.24$, $p<0.05$). DispAPPROACH was significantly correlated with BCPT at study entry, at 6 and 12 weeks ($r=-0.13–-0.19$, $p<0.05$) but not at 18 and 24 weeks. SitAVOID at all time points was significantly correlated with BCPT at all time points ($r=0.19–0.34$, $p<0.05$). SitAPPROACH at study entry was not related to BCPT any time point ($r=-0.00–0.09$, $p>0.05$). SitAPPROACH at 6 through 24 weeks was significantly correlated with BCPT at all time points ($r=0.11–0.29$, $p<0.05$), except SitAPPROACH at 6 weeks was not related to BCPT at 24 weeks ($r=0.11$, $p=0.27$). See Table S1 of the Electronic supplementary material for correlation matrices of relationships between SitAVOID and BCPT and Table S2 of Electronic supplementary material for relationships between SitAPPROACH and BCPT.

Overall Symptom Trajectory

As depicted in Fig. 2, the estimated mean BCPT symptom trajectory indicates that, on average, physical symptom bother increased slightly but significantly after diagnosis as indicated by the significant linear time trajectory ($b=0.04$, $p=0.003$). A significant negative quadratic time trajectory ($b=-0.01$, $p<0.001$) indicates that symptom bother plateaued over time and then decreased by 6 months. Deviance change tests

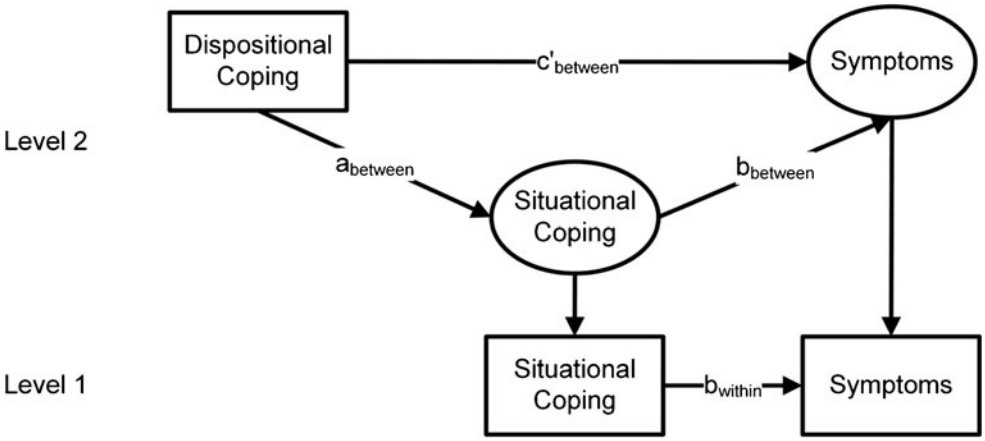

Fig. 1 Diagram of the 2-1-1 mediation model testing situational coping as a mediator of the relationship between dispositional coping and physical symptom bother

revealed significantly better model fit when including a random intercept (χ^2 (1)=405.65, p<0.001), random linear (χ^2 (2)=6.44, p=0.04), and random quadratic term (χ^2 (3)= 98.75, p<0.001), indicating significant differences in intercepts as well as linear and quadratic trends across women.

Covariates

Multilevel SEM models were fitted to assess levels of and changes in BCPT as a function of all demographic and cancer treatment-related variables. There was no significant effect of ethnicity, subjective social status, BMI, or cancer recurrence versus new diagnosis (all ps>0.05), and those variables were dropped. There were significant main effects of employment, education, marital status, stage, surgery type, chemotherapy, and radiation therapy (p<0.05), and they were retained as covariates. However, they did not predict the linear or quadratic time trend (all ps>0.05), and those higher-order effects were dropped. Income and recruitment site significantly predicted the intercept and linear time trajectory (p<0.05) and were retained as covariates. They did not predict the quadratic time trend (p>0.05), and those higher-order effects were dropped. Age, physical comorbidities, time of last treatment, estrogen antagonist use, aromatase inhibitor use, and herceptin use predicted the quadratic time trajectory (all ps< 0.05), and their effects on the intercept and quadratic and linear trajectories were retained as covariates.

Main Effect Models

As shown in Table 3, DispAVOID did not predict the linear or quadratic time trajectory for BCPT. A significant main effect of DispAVOID on the intercept of BCPT scores indicated that women who were higher in dispositional avoidance reported significantly higher physical symptom bother across study assessments (b=0.08, p<0.001). Effect size estimates indicate that the addition of DispAVOID to a model with only covariates resulted in a 12 % reduction in between-person residual variance (R^2=0.12).

DispAPPROACH significantly predicted the linear slope of the BCPT (b=0.01, p=0.01) and intercept (b=−0.12, p<0.001). Women who were higher in dispositional approach of emotion reported significantly lower physical symptom bother at study entry, but symptom bother increased more quickly for these women over time. The addition of DispAPPROACH to a model with only covariates resulted

Table 2 Means and standard deviations of major study variables at all assessment points (N=460)

Study variables	Study Entry *M* (SD)	6-Week *M* (SD)	12-Week *M* (SD)	18-Week *M* (SD)	24-Week *M* (SD)
BCPT total	0.83 (0.50)	0.80 (0.46)	0.85 (0.50)	0.79 (0.48)	0.76 (0.48)
SitAVOID	1.58 (0.39)	1.60 (0.37)	1.63 (0.39)	1.56 (0.38)	1.56 (0.39)
SitAPPROACH	3.20 (0.52)	3.14 (0.52)	3.11 (0.54)	3.05 (0.60)	3.01 (0.61)
DispAVOID	10.48 (4.85)				
DispAPPROACH	72.36 (21.43)				

BCPT Breast Cancer Prevention Trial Symptom Scales, *DispAVOID* dispositional non-acceptance of emotion, *DispAPPROACH* dispositional acceptance of emotion, *SitAVOID* coping through avoidance of the cancer experience, *SitAPPROACH* coping through approach of the cancer experience

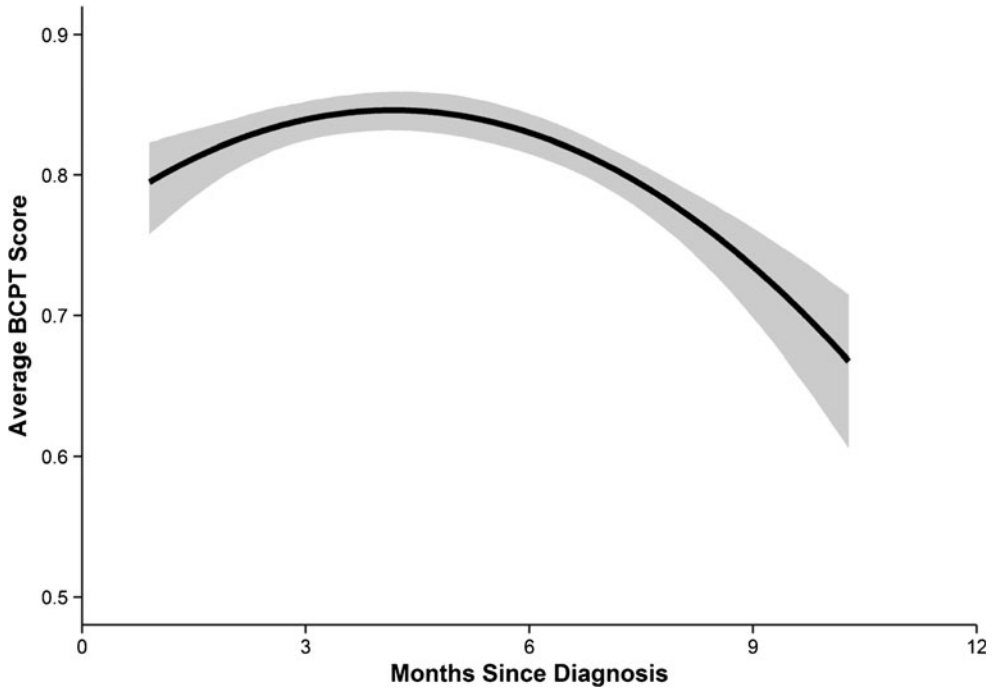

Fig. 2 Overall mean symptom trajectory for BCPT Symptom Scales

in a 6 % reduction in between-person residual variance (R^2= 0.06).

SitAVOID did not predict the linear or quadratic time trajectory of BCPT (all *p*s>0.05). However, a significant main effect of SitAVOID on physical symptom bother (b=0.15, p<0.001) indicated that for time points at which women endorsed more situational avoidance of cancer-related thoughts and feelings, they reported higher physical symptom bother. The addition of SitAVOID to a model with only covariates resulted in a 3 % reduction in within-person residual variance (R^2=0.03) and a 4 % reduction in between-person residual variance (R^2=0.04).

SitAPPROACH did not significantly predict the intercept, linear, or quadratic time trajectory for symptom bother (all *p*s>0.05). Post hoc analyses examining the six individual subscales that comprise the composite situational approach coping score revealed a significant positive main effect of seeking social support (b=0.03, p=0.04); at time points in which women endorsed more seeking of social support, they reported more physical symptom bother. Seeking social support did not significantly predict the linear or quadratic time trajectory of BCPT, and no other approach-oriented subscales significantly related to the intercept, linear, or quadratic time trajectory for physical symptom bother (all *p*s>0.05).

When entered simultaneously in the model, the effect of DispAPPROACH on the linear slope (b=0.01, p<0.001) and the main effects of DispAVOID (b=0.05, p=0.03), DispAPPROACH (b=−0.08, p=0.05), and SitAVOID (b= 0.13, p<0.001) all remained significantly associated with symptom bother in the directions identified in analyses of their separate main effects. All effects of SitAPPROACH remained non-significant (all *p*s>0.05). The addition of all dispositional and situational coping predictions to a model with only covariates resulted in a 9 % reduction in within-person residual variance (R^2=0.09) and an 11 % reduction in between-person residual variance (R^2=0.11).

Mediation Models

Mediation models were fitted to examine SitAVOID as a mediator of the relationships of DispAVOID and DispAPPROACH with BCPT. Because SitAPPROACH did not evidence a significant, direct relationship with BCPT, it was not examined as a mediator. MSEM included the same covariates and random effects as the primary main effect analyses. Standardized indirect effects are reported.

As depicted in Table 4, there was a statistically significant indirect effect of DispAVOID via SitAVOID on BCPT (*ab* [95 % confidence interval (CI)]=0.06 [0.03, 0.09]), accounting for 36 % of the total effect of dispositional avoidance on physical symptom bother. Greater dispositional avoidance predicted greater physical symptom bother directly as well as indirectly through greater use of situational avoidance coping. A statistically significant indirect effect of DispAPPROACH via SitAVOID on BCPT (*ab* [95 % CI]= −0.03 [−0.06, −0.01]) accounted for 17 % of the effect of DispAPPROACH on physical symptoms. Greater dispositional approach predicted less physical symptom bother through less use of situational avoidance coping (see Table 4).

It is also possible that dispositional coping strategies can moderate the effects of situational coping on physical

Table 3 Longitudinal growth models of the association of dispositional and situational coping with BCPT symptom scale total

	Coping measure			
Random effects	DispAVOID Est. (SE)	DispAPPROACH Est. (SE)	SitAVOID Est. (SE)	SitAPPROACH Est. (SE)
Intercept				
Intercept	0.67** (.22)	0.51* (0.24)	0.81*** (0.15)	0.80*** (0.15)
Chemotherapy[a] (ref=no)	0.04* (.02)	0.05* (0.02)	0.04* (0.02)	0.04* (0.02)
Endocrine therapy[a] (ref=no)				
Estrogen antagonists	0.04 (0.05)	0.16 (0.09)	0.04 (0.05)	0.04 (0.05)
Aromatase inhibitors	0.04 (0.05)	0.04 (0.10)	0.03 (0.05)	0.03 (0.05)
Surgery[a] (ref=no)	0.03 (0.02)	0.03 (0.02)	0.03 (0.02)	0.03 (0.02)
Radiation[a] (ref=no)	−0.05* (0.02)	−0.05* (0.02)	−0.05* (0.02)	−0.05* (0.02)
Herceptin[a] (ref=no)	−0.03 (0.04)	−0.20** (0.07)	−0.01 (0.05)	−0.02 (0.05)
Stage	0.01 (0.02)	0.01 (0.02)	−0.00 (0.02)	0.00 (0.02)
Employment (ref=employed)				
Retired	−0.07 (0.05)	−0.06 (0.05)	−0.08 (0.05)	−0.08 (0.06)
Unemployed	0.15** (0.05)	0.15** (0.05)	0.15** (0.05)	0.16*** (0.05)
Income	0.06** (.02)	0.06** (0.02)	0.04* (0.02)	0.04* (0.02)
Education	−0.04 (0.03)	−0.04 (0.03)	−0.01 (0.02)	−0.01 (0.02)
Married (ref=no)	0.06 (0.04)	0.07 (0.04)	0.07* (0.04)	0.06 (0.04)
Site (ref=Arizona)	0.19*** (0.05)	0.23*** (0.05)	0.16 (0.04)	0.20*** (0.04)
Age	−0.00 (0.00)	−0.00 (0.00)	−0.01*** (0.00)	−0.01*** (0.00)
Last treatment	0.01 (0.02)	0.01 (0.02)	0.03* (0.01)	0.03* (0.01)
Physical comorbidities	0.05* (0.02)	0.04 (0.02)	0.06*** (0.01)	0.06*** (0.01)
Coping	0.08*** (0.02)	−0.12*** (0.02)	0.15*** [a] (0.02)	0.01[a] (.02)
Linear trajectory				
Intercept	0.06 (0.06)	0.13 (0.24)	0.06 (0.06)	0.06 (0.06)
Endocrine therapy[a] (ref=none)				
Estrogen antagonists	−0.07* (0.03)	−0.08** (0.03)	−0.07** (0.03)	−0.07* (0.03)
Aromatase inhibitors	−0.01 (0.03)	−0.00 (0.04)	−0.01 (0.03)	−0.00 (0.03)
Herceptin[a] (ref=no)	0.06** (0.02)	0.11*** (0.00)	0.06 (0.02)	0.06** (0.02)
Income	−0.01** (0.00)	−0.01** (0.00)	−0.01* (0.00)	−0.01* (0.00)
Education	0.02* (0.01)	0.02* (0.01)	0.02* (0.01)	0.02 (0.01)
Site (ref=Arizona)	−0.01 (0.01)	−0.01 (0.01)	−0.01 (0.01)	−0.01 (0.01)
Age	−0.00 (0.00)	−0.00* (0.00)	−0.00 (0.00)	−0.00 (0.00)
Last treatment	0.01 (0.01)	0.01 (0.01)	0.01 (0.01)	0.01 (0.01)
Physical comorbidities	0.00 (0.01)	0.01 (0.01)	0.00 (0.01)	0.00 (0.01)
Coping		0.01** (0.00)		
Quadratic trajectory				
Intercept	−0.02 (0.01)	−0.01 (0.01)	−0.01 (0.01)	−0.02 (0.01)
Endocrine therapy[a] (ref=none)				
Estrogen antagonists	0.01* (0.00)	0.01* (0.00)	0.01* (0.00)	0.01* (0.00)
Aromatase inhibitors	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Herceptin[a] (ref=no)	−0.01** (0.00)	−0.01*** (0.00)	−0.01* (0.00)	−0.01** (0.00)
Education	−0.00 (0.00)	−0.00* (0.00)	−0.00* (0.00)	−0.00 (0.00)
Age	0.00** (0.00)	0.00** (0.00)	0.00** (0.00)	0.00** (0.00)
Last treatment	−0.00 (0.00)	−0.00 (0.00)	−0.00 (0.00)	−0.00 (0.00)
Physical comorbidities	−0.00 (0.00)	−0.00 (0.00)	0.00 (0.00)	−0.00 (0.00)

Table 3 (continued)

Random effects	Coping measure			
	DispAVOID Est.	DispAPPROACH Est.	SitAVOID Est.	SitAPPROACH Est.
$\sigma_{intercept}$	0.11	0.16	0.12	0.13
$\rho_{intercept,\ linear}$	0.00	−0.02	0.00	−0.00
σ_{linear}	0.00	0.01	0.00	0.01
$\rho_{intercept,\ quadratic}$	−0.00	0.00	−0.00	0.00
$\rho_{linear,\ quadratic}$	0.00	−0.00	0.00	0.00
$\sigma_{quadratic}$	0.00	0.00	0.00	0.00
$\sigma_{residual}$	0.05	0.05	0.05	0.05

Potential covariates not included due to non-significant prediction: ethnicity, new diagnosis versus recurrence, perceived social status, and body mass index

Est regression coefficient, *SE* standard error, *BCPT* Breast Cancer Prevention Trial Symptom Scales, *Coping* the coping variable used in each model as indicated by the column header, *DispAVOID* dispositional non-acceptance of emotion, *DispAPPROACH* dispositional acceptance of emotion, *SitAVOID* coping through avoidance of the cancer experience, *SitAPPROACH* coping through approach of the cancer experience

[a] Variable is time varying; all other variables are time invariant

*$p<0.05$, **$p<0.01$, ***$p<0.001$

symptom bother. However, we examined moderation and found no reliable evidence for it.

Post Hoc Analyses

Because time-varying situational coping was significantly associated with time-varying physical symptom bother, post hoc analyses were conducted to examine the prospective directional relationships between BCPT and SitAPPROACH and SitAVOID. A cross-lagged panel analysis [61] was used to investigate whether situational coping strategies were driving physical symptom bother or whether physical symptom bother was driving coping strategies. Four possible models of the relationship between situational coping (i.e., SitAPPROACH and SitAVOID) and BCPT were compared to identify the best fitting model. These models include the following: (M1) only the autoregressive paths of BCPT, SitAVOID, and SitAPPROACH at all time points; (M2) the autoregressive paths and paths predicting BCPT from SitAVOID and SitAPPROACH; (M3) the autoregressive paths and paths predicting SitAVOID and SitAPPROACH from BCPT; and (M4) a combination of M2 and M3. Variables at the initial time point and error terms associated with variables at later time points were freely covaried within a time point. Within a variable, heterogeneous residual variances were allowed across time but were assumed independent over time. Examination of separate models for approach and avoidance coping did not reveal substantial differences in the effects of specific coping on physical symptom bother or physical symptom bother on specific coping, so only the models combining the two are presented here.

Chi-squared difference tests revealed that, compared to the autoregressive only model (M1), there was a significant improvement in fit adding cross-lagged paths from coping to physical symptom bother (M2; χ^2 (8)=20.87, p=0.01). Similarly, compared to M1, adding cross-lagged paths from physical symptom bother to coping significantly improved model fit (M3; χ^2 (8)=46.01, $p<0.001$). The model with bidirectional cross-lagged paths (M4) fit significantly better than M2 (χ^2 (8)= 45.44, $p<0.001$) and M3 (χ^2 (8)=20.31, p=.01), indicating that a model with bidirectional cross-lagged paths between situational avoidance- and approach-oriented coping and physical symptom bother best fits the data (see electronic supplemental material for model fit statistics and model comparisons).

Discussion

The experience of breast cancer substantially impacts physical health and functioning [33], and the present findings indicate that, consistent with previous research [4, 6], dispositional and situational coping have unique importance for predicting bother from physical symptoms following breast cancer diagnosis. Findings not only provide support for the main effects of dispositional and situational coping on physical symptom bother but also for the mediating role of situational avoidance coping on the relationship between dispositional coping and symptom bother.

Table 4 Indirect effects of DispAVOID and DispAPPROACH on outcomes via SitAVOID and SitAPPROACH on BCPT Symptom Scales total

		Predictor	
		DispAVOID	DispAPPROACH
Mediator	Parameter	Est. [95 % CI]	Est. [95 % CI]
SitAVOID	Direct	0.10* [0.03, 0.18]	−0.17* [−0.25, −0.09]
	Indirect	0.06* [0.03, 0.09]	−0.03* [−0.06, −0.01]
	Total	0.16* [0.09, 0.23]	−0.20* [−0.28, −0.12]
	Ratio	36.05 %	16.54 %

Results are reported based on standardized variables

Est estimated effect, *95 % CI* 95 % credible interval based on Bayesian multilevel structural equation model, *indirect* ($a_{between}$*$b_{between}$), *total* (indirect + direct), *ratio* percentage of total effect that is mediated, *BCPT* Breast Cancer Prevention Trial Symptom Scales, *DispAVOID* dispositional non-acceptance of emotion, *DispAPPROACH* dispositional acceptance of emotion, *SitAVOID* coping through avoidance of the cancer experience, *SitAPPROACH* coping through approach of the cancer experience

*$p<0.05$

Main Effect Models

Present findings largely support the hypothesized main effect model of dispositional and situational coping on physical symptom bother, in which both dispositional approach and avoidance and situational avoidance independently predicted concurrent and later physical symptom bother. Consistent with hypotheses, dispositional avoidance of negative emotions predicted more physical symptom bother throughout the 6 months after diagnosis. This finding is consistent with past research suggesting that dispositional avoidance of emotions, bodily sensations, memories, and/or behaviors predicts lower quality of life [62], as well as physical health risk (e.g., cardiovascular risk) and problematic health behaviors [63].

Also consistent with hypotheses, dispositional approach of emotions predicted less physical symptom bother at study entry, approximately 2 months after diagnosis. This is in accordance with past research, which has demonstrated that dispositional acceptance of emotions predicts less distress in women with breast cancer [43]. Although women high in dispositional approach had less physical symptom bother shortly after diagnosis, their symptom bother increased more quickly over time. This finding suggests that the buffering effect of dispositional approach is strongest in the months immediately following diagnosis during active breast cancer treatment. In light of the cumulative physical side effects of breast cancer treatments, acknowledging, as compared to repressing, emotional distress may result in reports of greater bother over the trajectory of treatment [64].

As hypothesized, situational avoidance of the cancer experience in the months following breast cancer diagnosis predicted more physical symptom bother. These findings expand upon research that demonstrates a relationship between situational avoidance and poor psychological adjustment to breast cancer [9, 15, 18] by revealing a relationship between situational avoidance and physical symptom bother. It is possible that women who experience more bother from physical symptoms may feel compelled to employ more situational avoidance coping compared to women who experience less bother from symptoms. To address this possibility, we conducted cross-lagged panel analyses, which demonstrated that including all bidirectional cross-lagged paths improved the fit of the model. It appears that situational coping predicts physical symptom bother and vice versa.

In contrast to previous research [25, 26, 64, 65], situational approach of cancer-related thoughts and feelings was not associated with physical symptom bother in the multilevel models with covariates. Although previous research reveals that coping with cancer through approach relates to improved psychological adjustment [25, 26, 65, 66], more research is needed to understand its relationship to physical symptom bother. Why might using approach-oriented coping strategies be unrelated to physical symptom bother? Approach-oriented coping may relate more consistently to positive indicators of adjustment (e.g., positive affect and personal growth) than negative outcomes (e.g., physical symptom bother and psychological distress). In their review, Taylor and Stanton [8] note that relationships between approach coping and adjustment are more inconsistent than avoidance and suggest that the mixed findings might be partially driven by studies focusing on maladjustment.

When dismantling the composite situational approach measure, seeking social support was the only subscale with a significant main effect on physical symptom bother. Greater coping with cancer through social support predicted more bother from physical symptoms. Although perceived social support typically relates to better adjustment to stress [67], this is a measure of *seeking* social support and could be capturing the need for greater support at times of higher symptoms, such as during treatment with chemotherapy. Additionally, consistently seeking social support could represent low cancer-related self-efficacy, which relates to poor adjustment [68].

Mediation Models

Beyond main effects, the present findings are also consistent with a hypothesized mediation model of coping. Dispositional avoidance of emotions predicted increased cancer-related avoidance, which in turn predicted more physical symptom bother. Dispositional approach also predicted less physical symptom bother through less use of situational avoidance. The present findings are consistent with Moos and Holahan's [7] proposed theoretical model which suggests that dispositional factors can influence adjustment to stress both

directly and indirectly through situational factors. Further, the findings are in line with research evidencing the dispositional underpinnings of situational coping strategies [69, 70] and previous literature investigating situational coping as a mediator of the relationship between dispositional attributes and adjustment to breast cancer [9]. The findings indicate that dispositional coping preferences may predict the selection of later situational coping strategies, which in turn is associated with physical symptom bother.

Limitations and Strengths

Although this is the first study to our knowledge to assess the unique and shared predictive power of situational and dispositional avoidance and approach on bother from physical symptoms, several limitations should be considered. The present study examines dispositional avoidance and acceptance of emotional experiences; future research should investigate the relationship between dispositional behavioral and cognitive avoidance (e.g., denial and distraction) and approach (e.g., reappraisal and problem solving) coping strategies and physical symptom bother. A second limitation is that the current study only investigates one dispositional factor. Other dispositional intrapersonal factors also may be associated with symptom bother (e.g., neuroticism and mastery). The present study also is limited in that the dependent variable was a negative indicator of physical health-related adjustment; positive indicators of physical adjustment such as energy might have exhibited a stronger association with approach-oriented coping. Furthermore, the dependent variable was how much bother women experienced from the physical symptoms related to their cancer treatment. More objective measures of health (e.g., doctor's visits and markers of inflammation) might exhibit different associations with dispositional and situational coping. Additionally, the measures used in the present study have not been formally normed on breast cancer patients. Women completed measures independently on a computer or in interview format, which may differ in terms of social desirability, which we could not test adequately in the present study. A prospective study design in which measures of dispositional coping are assessed prior to diagnosis would have been ideal. This sample was comprised of predominantly non-Latina white women, and findings might not generalize to breast cancer patients of other ethnicities. However, approximately 20 % of the current sample is Latina, which is representative of the geographic locations of the breast cancer clinics from which participants were recruited, and ethnicity was not related to physical symptom bother.

Strengths of this research include using distinct measures of situational and dispositional coping rather than the same items with different instructions, so as not to inflate correspondence between the constructs. Additionally, the use of a relatively large sample, missing data model, and multilevel modeling allows for the examination of levels of physical symptom bother through the first 6 to 9 months of the cancer experience. Furthermore, post hoc analyses, which demonstrated reciprocal relationships between coping and physical symptom, bother address concerns about reverse causality.

Despite limitations of the present work, the findings provide support for the direct and mediated relationships of dispositional response to emotion and situational cancer-related coping with bother from treatment-related physical symptoms. The current study suggests that dispositional approach of emotional experiences is more beneficial than situational approach for lessening physical symptom bother following breast cancer diagnosis, whereas both dispositional and situational avoidance have deleterious implications for symptom bother. These findings suggest that individuals high in dispositional approach are more resilient against bother from symptoms related to breast cancer treatments, at least initially. Additionally, findings suggest that coping skills training should be targeted toward dispositional avoiders and aimed at reducing situational avoidance. Although replication is needed, it appears that not all forms of cancer-specific approach might be useful in reducing symptom bother. Decreasing avoidance and facilitating approach of emotions are main ingredients in a recent unified protocol for treating emotional disorders [71]. Interventions based on such protocols may be particularly beneficial for the physical well-being of women with breast cancer. These findings are important in light of the evidence that physical side effects of cancer treatment (such as fatigue and pain) are debilitating morbidities [72]. Intervening with individuals high in dispositional avoidance, and/or low in dispositional approach, and targeting maladaptive avoidance coping could carry significant benefit for the health and functioning of individuals diagnosed with cancer or confronting other chronic stressors.

Acknowledgments We are thankful to the women who participated in the My Year After Breast Cancer study, as well as to the referring oncologists.

Sponsors Supported by 1R01 CA133081 (Stanton & Weihs, co-PIs), NCI P30CA023074–University of Arizona Comprehensive Cancer Center Support Grant, (Weihs, PI Alberts) National Science Foundation Fellowship (Bauer, DGE-1144087), National Institute of Mental Health Predoctoral Fellowship (Harris, MH 15750), Jonsson Comprehensive Cancer Center support grant, NIH/NCI P30 CA 16042 (Crespi, PI Gasson).

Compliance with Ethical Standards

Authors' Statement of Conflict of Interest and Adherence to Ethical Standards Authors Bauer, Harris, Wiley, Crespi, Krull, Weihs, and Stanton declare that they have no conflict of interest. All procedures, including the informed consent process, were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

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